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ADVANCE IN KNOWLEDGE OF CANCER

(*The Editor of* Nature *has kindly allowed the Committee of the Research Defence Society to reprint for the Society's use the following article by Dr. Bashford, Director of Imperial Cancer Research. Dr. Bashford, also, has kindly agreed to let the article be thus used.*)

In conformity with a scheme of inquiry embarked upon in October, 1902, the third scientific report of the Imperial Cancer Research Fund, recently issued, treats, like its predecessors, of cancer as a problem of general and experimental biology. It contains no definite answer to the questions, What is the nature and what the cause of cancer ? and beyond demonstrating that systematic experiment justifies the early surgical removal of a tumour as the only possible treatment at the present time, the report is silent as to remedial and preventive measures. These shortcomings will almost certainly arouse misgivings on the part of those who cannot appreciate how progress is made in any field of knowledge. They will also, no doubt, be seized upon by persons who, in their ignorance, assert that all scientific efforts should be concentrated on utilitarian ends, and they will be exploited by the charlatan, to whom for a space a free field is still left for his nostrums. The sustained efforts of the past six years to penetrate the mysteries of cancer have been accompanied by a corresponding activity on the part of faddists and quacks who advertise themselves by proclaiming the failure of scientific investigation to yield "practical fruits." The danger of their literary activity is but enhanced by the powers of diction and of exposition possessed by some of the writers. They could profitably devote their literary ability to expounding to the public the true facts and difficulties of the cancer problem, instead of the ridiculous causes they maintain before a jury of the credulous and the suffering. In the absence of this enlightened attitude on their part, it is my duty, since the second scientific report was followed by volumes of nonsense on the part of such persons, bluntly to inform the general reader of the folly of ignoring the necessity for the early surgical removal of cancer, and of running from one faddist or quack to another yet more ignorantly sanguine. If, in the future, the progress of scientific investigation provides a substitute for or an adjunct to surgical treatment, there will be no needless delay in placing it within the reach of the cancer patient.

Meantime, the importance of the investigation of cancer is only too grimly emphasised by its frequency as a cause of death. The number of deaths *recorded* from cancer increases from year to year throughout the world, civilised and uncivilised, human and animal. Taking England and Wales as an example, in 1889, on an average, the chance of a man above thirty-five years ultimately dying of cancer was one in twenty-one, and for a woman above the same age one in twelve. The increase in the number of deaths *recorded* from cancer makes the corresponding chances to-day one in eleven for men and one in seven for women. Scarcely a family of large size escapes attack. There is no circle of acquaintances, no chance assemblage of persons at a *table d'hôte* or in a tube lift, but contains prospective victims. But is cancer really increasing? The accurate use of statistics, and the careful scrutiny of scientific value of the data upon which they are based, still withhold an affirmative answer. If it be further asked, Is not cancer much more frequent in races living under European civilisation than in the rest of mankind? recent investigation has disposed of the fiction that many races of mankind are exempt. Where the disease was said to be rare—*e.g.*, in Japan—there are excellent statistics, of which Europeans were previously ignorant, proving the great frequency of cancer among the Japanese; and, taking another example, investigations in Indian hospitals show that certain forms of cancer very common in London hospitals are probably not less common in hospitals throughout Hindustan. In the case of most other races there are insurmountable difficulties in the way of even thus roughly estimating its frequency among them. Therefore it is idle to affirm or to deny that cancer may be more common in some races than in others. The disease occurs throughout the human race, and its association with forms of chronic irritation having nothing in common beyond this association is a fact of more moment than any futile discussion of the relative liability of different races. The additions, during six years, to our knowledge of its occurrence in man, as well as in tame and wild animals, tell hard against those who, at the close of the nineteenth century, argued that the increase in the number of deaths attributed to cancer was real, and merely a penalty for living under the influences of European civilisation.

Much additional evidence has been obtained of the extent to which cancer pervades the vertebrate scale. The similarity of the disease thoughout vertebrates is illustrated most diagrammatically by a series of preparations of skin-cancers from mammals to marine fish living in a state of nature. Wherever data are available, for animals as for man, the liability to cancer is shown to be greatest in the last third of the span of life, whether it be short or long; the "age-incidence" of cancer in man has acquired enhanced significance by the establishment of this generalisation.

The widening of our knowledge of the occurrence of cancer is only one example of how revived interest in mere observation has put an end to the era of unverified, and often unverifiable, speculation which characterised the last twenty years of the nineteenth century, when exact methods of studying the clinical course, the anatomy, and the microscopical structure of tumours had reached their natural limitations. The study of cancer solely from the standpoint of its being an infective disease had yielded equivocal and self-contradictory results. Statistical methods had become barren from want of data to work on. No point vulnerable to an attack in the rear by the experimental method could be discerned.[1] In short, there was a standstill in the advance of knowledge. As is usual in all similar epochs in the progress of science, observation, hypothesis, and experiment had ceased to advance hand in hand. The armchair speculator had the field to himself. With only the knowledge derived from the bedside, the study of the structure of tumours in man, imperfect data of its incidence in Europeans, and hearsay statements of its absence elsewhere to guide him, he little comprehended the futility of the explanations he so lightly advanced, and others of his kind equally lightly refuted. A general feeling of the hopelessness of penetrating to the truth was abroad, both among the public and the medical profession, who, the limits of surgical aid having been reached, were despondent in the extreme. The universality of this conviction led to the spontaneous and independent formation of "cancer research committees" in different countries at the end of the nineteenth century.

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[1] As a matter of fact, such a point of attack had existed since the time when Hanau and Morau had successfully inoculated cancer from one animal to another, but those engaged in cancer research had either failed to realise the significance of this imperfect work or had been baffled by the difficulties which had to be overcome in attempting to imitate it.

The whole outlook of the cancer question has been changed by the successful application of the comparative biological and experimental methods to its study, and by the restoration of the legitimate relations of observation, speculation, and experimental verification. In this revival the committees formed in different centres have played very unequal shares, according as their proceedings have conformed to the methods which advance natural knowledge. To demonstrate fully the adequate evidence upon which the claim—cautiously advanced in the first and second scientific reports and earlier papers—is based, that a new and rational era of investigation has been inaugurated, and to urge continued confidence in the investigation of cancer, are the primary objects and the main justifications of the third scientific report of the Imperial Cancer Research. The time has not come when practical applications of the additions to knowledge are to be expected, nor has accident yet yielded any

Although the rapid accumulation of new facts forbids the premature formulation of a generalisation attempting a unification of the mass of new and old knowledge, many results of far-reaching importance have been attained. The work of recent years has made it more certain than it ever was before that cancer contains no virus or other parasite foreign to the living organism. One is often asked if a relative suffering from cancer is dangerous to others—*e.g.*, a grandmother to her grandchild, the chief solace of her old age—or if an historic family mansion should be burnt down because many progenitors inheriting it had died of cancer. During six years many tens of thousands of mice suffering from cancer have been under the most stringent observation. If cancer were communicable in the sense in which infective diseases are communicable, animals housed along with those naturally suffering from, or inoculated with, cancer would be the first to suffer. In an experience extending over six years, *i.e.*, almost three times the average length of a mouse's life, exhaustive investigation has shown that this risk does not exist. This fact of itself satisfies those handling the animals. They incur still less risk in passing many hours daily dealing with cancerous animals in a room in which 10,000 of such mice and rats are usually housed at one time. If such a "cancer house" as never before existed has no dangers to human beings who spend their days in it, *a fortiori* other persons have no ground for apprehension. These results are of great practical value. They reinforce opinions often expressed in the past for other reasons. The presence, every day in the year, of some 50,000 persons suffering from cancer in England and Wales constitutes no menace to the health of those near and dear to them, nor to the health of the population generally, as would a smaller number of people suffering from smallpox. Notwithstanding the unwise assertions irresponsible enthusiasts will continue to make from time to time, what was a justifiable cause of public alarm has been removed by experiments on the transference of cancer from one animal to another, and on the housing of large numbers of cancerous with sound animals over a prolonged period. It has been demonstrated completely that artificial transference from animal to animal is due to the implantation of living cells. This is a factor which does not come in at all in reference to the frequency of spontaneous cancer in man or animals. In corresponding observations on mice suffering from spontaneous cancer no case of transference has occurred.

In this respect cancer presents a marked contrast to other diseases—*e.g.*, tuberculosis—equally widely disseminated and common to man and the whole vertebrate phylum, for although no race of mankind is exempt, and cancer extends down the vertebrate scale to marine fish living in a state of nature, there are the most striking limitations to its communication from one individual to another. There is no connecting link, as it were, between the disease as it presents itself in nearly allied species, nor yet even in individuals of the same species. There is nothing which, while foreign to the animal body, is nevertheless common to cancer wherever it occurs. There is nothing equivalent, *e.g.*, to the characteristics of tuberculous tissues which, no matter what the species of animal, are stamped with unmistakable common features by the presence of the tubercle bacillus. The properties of the tubercle bacillus obscure all the natural properties of the tissue containing it, and they confer upon such tissue new properties essentially the same in all species of animals. Tubercular tissue has common properties in all animals; the distinctions of species, and of individual tissues of one and the same species, are submerged in their acquirement of a new property, conferring on them the power of conveying the disease to previously healthy tissues, not only from one animal to another of the same species, but also to others of different species. The tuberculous *tissues* themselves, however, die when transferred to a new animal; they do not grow, they merely hand on the cause of the disease, viz., the bacteria, which continue to grow in new soil. How, then, is the pervasion of the animal kingdom by cancer explicable? It is intelligible because experiment has proved that cancerous tissues retain, not only the characters of the species of animal, but also those features distinguishing the several normal tissues of an individual, and because the general conclusion from comparative and experimental investigation is that cancer arises *de novo* in each individual attacked, by a transformation of healthy tissue, one case of cancer having no relation to any other. This general conclusion is based upon observations and experiments of very varied but confirmatory nature.

When a piece of cancer-tissue of a mouse is implanted into another mouse, certain of the cells continue to grow in the new animal and others die. The cells which continue to grow are the cancer cells proper. The other cells which die formed the scaffolding of supporting connective tissues and blood-vessels. The process of transference can be repeated *ad infinitum*, the powers of growth of the cancer cell being inexhaustible; they set at defiance the laws determining the specific sizes of the bodies and the organs of vertebrates, and determining the specific duration of the lives of different vertebrates. The cancer cells retain their characters unaltered in the course of artificial propagation, and the connective tissue scaffolding, supplied afresh by each successive host, remains identical with that which the cancer cells had in the animal where they originated. This scaffolding is called forth by the cancer cells themselves, and is of the nature of a specific reaction on the part of the ordinary connective tissues and blood-vessels of the host. The scaffolding is characteristically different for different tumours, and, as will be stated below, the cancer cell is unable to continue to live and grow without it. The propagation of cancer is only possible in animals of the same species—*e.g.*, from mouse to mouse, or rat to rat, but not from mouse to rat or *vice versa.*

Since the limits to transplantation are the same as those which limit the transplantation of normal tissues—*e.g.*, the grafting of skin—the facts are of themselves evidence that cancer tissue contains nothing extraneous to the animal in which it appears. The distinctive differences in the new scaffolding which different tumours even of the same organ—*e.g.*, the mamma—re-acquire after every transplantation are inexplicable on the assumption that the tumour cells contain a common virus endowing them with their peculiar properties. Thorough investigation of questions of metabolism has shown the relations of a tumour to its host to be merely those of nutrition, similar to those of the fœtus *in utero* to its mother. More than seventy transplantable tumours of very varied nature have been studied in the laboratory, and the above facts hold for them all.

The features of growth and of histology exhibited by different spontaneous tumors remain distinctive in the course of continued propagation, and they give weighty indications of the nature of the changes responsible for the acquisition of cancerous properties, since there is neither progress to a uniform histological structure nor a gradual advance to the exhibition of uniform biological behaviour, nor acquisition of a uniform rate of growth. The transformation of normal into cancer cells really covers a scale of changes which do not pass into one another. Permanent features are stamped upon cancer cells at the outset. There is no transition from one degree of the cancerous change to another.

In the transplantation of a tumour into a new host, success or failure is determined primarily by two factors. These are the qualities of the tumour cells, and the nature of the "soil" the new animal offers. During continued propagation, the cells of the tumours of a single organ—*e.g.*, the mamma—exhibit other differences corresponding to those mentioned above with reference to the "supporting" scaffolding, and together with them pointing still more strongly to primary qualitative differences in the cells of different tumours. Although cancer occurs spontaneously mostly in old animals, young animals are more suitable for growth. The introduction of a minute particle of cancerous tissue into a normal animal leads to all the consequences which accompany the growth of a spontaneous tumour. Thus the adequacy of the assumption with regard to man, that the origin of cancer is primarily circumscribed, is demonstrated. A consideration of all the results proves that the genesis of a tumour and the growth of a tumour are two different things.

The "soil" which different races of mice offer, as it were, for the growth of cancer varies naturally in suitability; but tumours can gradually or rapidly adapt themselves to a soil which was unsuitable; *e.g.*, when a Danish tumour was first transplanted in England it grew in only 5 per cent. of the mice inoculated, but later the success rose to 90 per cent. There are natural constitutional conditions which are favourable, and others which are unfavourable, to the growth of a tumour. The unfavourable conditions act as sieves, permitting certain kinds of cells to pass, and once they have passed they can multiply beyond our powers of measurement.

The "soil" can, however, also be modified experimentally. It can be made absolutely unsuitable for growth, or rendered more suitable than normal

Mice and rats can be rendered unsuitable for growth only by vaccinating them with malignant new growths of their own species, and by vaccinating with *normal* tissues of their own species. In the latter case the degree of "resistance" normal tissues produce directly corresponds to the closeness of the relationship between the normal tissue vaccinated and the tumour subsequently inoculated; *e.g.*, skin protects best against skin cancer. These facts refer us back again to the limitations to the transplantation of tumours, and together with them demonstrate the retention, by malignant new growths, not only of the tissue characters of a species, but also of the biochemical as well as of the histological characters distinctive of the several species. A sarcoma of a rat or cat, vaccinated into a mouse, lacks the power of protecting it against subsequent inoculation of a mouse sarcoma; this fact shows, as clearly as the method permits, the absence of any extraneous agent common to the growths of these different species. The growths of different species of animals resemble one another just as much, and differ just as much, as their respective organs and tissues do. As differences exist in certain properties of tumours already alluded to above, so corresponding other differences are revealed by the extent to which tumours, when vaccinated, induce protection against one another. A tumour does not vaccinate so well against other tumours as it does against itself or against those of its own kind. A lesser degree of protection which one kind of mouse-tumour induces against other kinds is due, probably, not to cancer-tissue as such, but to its properties *qua* mouse-tissue.

Animals which are absolutely protected against inoculation do not yield a serum which, when introduced into new animals, has a power of protecting them against inoculation; still less is there any evidence of immune sera having a power to cure animals of tumours already growing. Highly immune mothers do not transfer immunity to their offspring as do animals immune to diphtheria or other poison of infective disease. Indeed, the mechanism of the protection which can be induced against cancer is of a kind quite unknown before. Most painstaking observations have been necessary to penetrate somewhat into its nature. Artificially protected animals do not supply the cancer cell with the peculiar scaffolding of supporting tissues it requires in order to grow into a tumour. It dies because it cannot grow into an organised tissue, and hence cannot nourish itself; being damaged, it falls a prey to the natural guardians—the phagocytes—of the body. The process is the same whether vaccination has been made with cancer or with normal tissue. The way in which this protection becomes general in the body fluids or tissues has not yet been fully ascertained; nevertheless, so far as it is known, it helps to elucidate the spontaneous healing of primary and secondary growths in man, and its further study gives promise of our being able ultimately to enhance the powers of resistance of the body to a degree which will prevent the dissemination of a primary growth.

Before so much can be attained there are many difficulties to be overcome, not the least of which is the discovery of the fact mentioned above, that the soil may be rendered more than normally suitable for the growth of cancer. Hypersensitiveness can be induced by many different agencies; indeed, as contrasted with the induction of protection, it is not specifically induced.[1] The growth of one tumour does at times make the "soil" of an animal more favourable for the growth of a second tumour, and therefore, presumably, for dissemination. It is much more difficult to protect an animal already bearing a tumour against the transplantation of a second tumour than it is to protect an animal which has not already got one.

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[1] The variety of the agents which render an animal hypersensitive for the growth of cancer acquires added interest when regarded in association with the variety of causes of chronic irritation related to the development of cancer in mankind, as referred to above.

Animals spontaneously attacked with cancer make efforts, which are sometimes successful, to cure themselves both of primary and of disseminated growths; *e.g.*, in the vessels of the lungs. There is no longer room for scepticism regarding the statements which have been made from time to time of similar occurrences in man. The process of spontaneous healing is much more common in animals bearing transplanted tumours. In their case it can be studied in great detail, and it has been found to follow the same course as in man. A weighty factor contributing to its occurrence resides in the properties of the cancer cells themselves, for it has been discovered that they multiply with unequal rapidity at different times. They alternate regularly between positive and negative phases of growth. They are much more vulnerable to attack in the negative phase; *e.g.*, through the heightened unsuitability or resistance which can be induced in the soil as described above. The further study of the relations obtaining here will ultimately assist us to prevent a primary tumour from disseminating and establishing offshoots in remote parts of the body.

A startling phenomenon has been stumbled upon during the artificial propagation of epithelial malignant new growths (carcinomata). In the course of time some of these tumours have been replaced by connective tissue new growths (sarcomata). There is no question of the conversion of epithelial into connective tissue cells.

All the facts point to the acquisition of cancerous properties by what were previously normal connective tissues, viz., cells of the supporting scaffolding or "stroma." It appears probable that in this way malignant new growths have been produced for the first time experimentally. The development of sarcoma in this way occurs in circumstances throwing much light upon why cancer in man is so frequently associated with chronic irritation, as referred to above, and resulting continuous or intermittent attempts at regeneration and repair in man. Together with other facts, notably the differences in incidence of cancer in different races of mankind as determined by the application of irritants to different parts of the body, it gives the *coup de grâce* to the generalisation of the idea that cancer is of congenital origin.

Many new facts recorded above are of fundamental importance in enabling us better to comprehend the nature of cancer. Two factors have been proved to be of prime importance in its development; one is the alteration within a circumscribed area of what were normal into cancerous cells, either under the influence of unknown causes in the body itself or through the mediate intervention of diverse external chronic irritants, which may be actinic, chemical, bacterial, mechanical, in short, are legion; the other factor is the constitutional condition of the living body which may favour or hinder growth of the limited number of altered cells into a tumour. Extensive observations on inbreeding stocks of cancerous mice show that inborn predisposition plays only a very subsidiary, if any, part in determining both the one and the other; both are acquired. Cancer is a foe to all men, and the liability to it being in all probability acquired may ultimately be found to be avoidable.

A sudden revolution of all former views on the nature and treatment of cancer has not been effected. Much of the knowledge inherited can be utilised, much of it must be discarded. I have not dwelt on the initiative, the sacrifices, and the patient toil of my colleagues Bowen, Cramer, Gierke, Haaland, Murray, and Russell, nor on the enlightened and generous encouragement of the executive committee of the Imperial Cancer Research. It will be evident to all who read my colleagues' papers in the report how much they have contributed to raise the British national investigations of cancer to the premier position among similar institutions abroad. I have not made reference to work by other distinguished investigators, but full credit is given to them in the report itself. Slowly feeling the way from one certain step to another has often simply meant being met by new and unsuspected difficulties. Each hitherto unsuspected difficulty when overcome has, however, brought us more nearly face to face with the realities of cancer genesis, cancer growth, and the natural means by which the body protects itself against them ; they all are better comprehended and nearer solution to-day than ever before.

E. F. B.